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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/689,430	10/12/2000	Christopher E. Walsh	35052/204373 (5052-53)	7095

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EXAMINER

LI, QIAN JANICE

ART UNIT PAPER NUMBER

1632

DATE MAILED: 10/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/689,430

Applicant(s)

WALSH ET AL.

Examiner

Q. Janice Li

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 July 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6, 8-12, 14-20, 58-77, 79-88 and 90-92 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-12, 14-20, 58-77, 79-88, and 90-92 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12 June 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

The response filed on 7/14/04 has been entered. No claim is further amended. Claims 1-6, 8-12, 14-20, 58-77, 79-88, and 90-92 are pending and under current examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3-6, 8-12, 14-18, 20, 58-77, 79-88, and 90-92 stand rejected under 35 U.S.C. 103(a) as unpatentable over *Gnatenko et al* (1996, IDS/85), *Dwarki et al* (US 6,221,646), *Dwarki et al* (1995, IDS/15), in view of *Carter et al* (US 5,866,696), *ILL et al* (US 5,744,326), and evidenced by *Vorachek et al* (J Bio Chem 2000 Sep;29031-41).

In the 7/14/04 response, applicants first argue that there is no motivation or suggestion to combine the cited references.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, *Gnatenko et al* clearly teach the use a recombinant AAV vector comprising a *B-domain deleted* factor VIII for hemophilia A gene therapy, *Dwarki et al* supplemented the teaching of *Gnatenko et al* by a showing of combined use of an AAV ITR (column 5, lines 3-4) and other liver-specific expression elements (e.g. an AFP enhancer and albumin promoter, column 6, line 35) for expression of the B-domain deleted factor VIII (column 9, line 44), these teachings established the levels of the skilled in the art with respect to expressing B-domain deleted factor III by actual reduction to practice concerning constructing a recombinant AAV, and such practice clearly suggests to the ordinary skilled that it is desirable and common in the art to use rAAV for factor VIII expression. The above teaching however did not disclose the use of AAV ITR as the sole promoter.

The deficiency was supplemented by *Carter et al* who particularly teach that the AAV ITR itself is sufficient as a transcription promoter for expression of a heterologous therapeutic gene in human cells, and provide clear motivation for doing so, which is cited in the previous Office action, i.e. it is important and desirable to obtain smallest possible regulatory elements because of the size limitation of the AAV vector.

ILL et al was cited to supplement the above teachings concerning a particular liver-specific enhancer for expressing a B-domain deleted FVIII at therapeutic levels (Fig. 6). Such teaching regarding improvement of expression levels would have suggested to the ordinary skilled that it is desirable to include such element for enhanced expression.

The instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Given the teaching of the prior art concerning the rAAV expression vector, B-domain deleted FVIII, and regulatory elements-all taught to be useful for constructing a rAAV vector for sufficiently expressing a heterologous gene at a therapeutic level, it would have been *prima facie* obvious to one of ordinary skill in the art to combine these elements to generate a new rAAV construct for the treatment of hemophilia with a reasonable expectation of success.

Applicants then allege that the rejection combined the reference with impermissible hindsight vision.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the conclusion is established solely on the knowledge at the

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time before the claimed invention was made, and does not rely on applicant's disclosure, and accordingly is proper.

Applicants then argue that the art teaches away from the claimed invention because in the previous response, Applicant's cited Zhang reference teaching that AAV ITR is a weak promoter.

In response, the teaching of *Zhang et al* has been addressed by the cited reference of *Carter et al*, who clearly aware of the opinion in the art, and particularly teach that contrary to the conventional wisdom, they discovered that if a AAV vector carrying a therapeutic gene such as CFTR is placed immediately adjacent to the AAV ITR, it can be functionally expressed in human cells to correct the related physiological defect such as cystic fibrosis. *Carter et al* also teach that it is desirable to use the AAV ITR rather than the usual AAV p5 or other promoter because the size limitation of AAV vector (column 2, lines 19-49).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector taught by *Gnatenko et al*, to include the elements as taught by *Dwarki et al*, *Carter et al*, *ILL et al*, so that the expression vector would be more efficient for hemophilia A gene therapy with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed vector because given the numerous teachings in the art regarding various elements making the vector more efficient and suitable for gene therapy, it falls within the bounds of optimization for the ordinary skilled to make an efficient expression vector. Further, given the effectiveness of the expression vector elements disclosed in

individual references, the ordinary skilled would have had a reasonable expectation of success when combining the elements to make a new vector. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

Thus, the rejection stands.

Claims 2 and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Gnatenko et al* (1996, IDS/85), *Dwarki et al* (US 6,221,349), *Dwarki et al* (1995, IDS/15), *Carter et al* (US 5,866,696), and *ILL et al* (US 5,744,326) as applied to claims 1, 3-6, 8-12, 14-18, 20, 58-77, 79-88, and 90-92 above, and further in view of *Gao et al* (US 6,258,595).

Applicants assert that there is no teaching in *Gao et al* that the ITR could be used as the only promoter to drive expression of B-domain deleted FVIII nor motivation to combine.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the use of AAV ITR as the only promoter was taught by *Carter et al* as discussed in the immediate preceding rejection, and the motivation to

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combine the spacer as taught by *Gao et al* is to optimize the expression level of the rAAV. It is noted, that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988).

Accordingly, the rejection stands.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

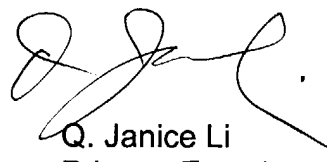
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Q. Janice Li
Primary Examiner
Art Unit 1632



September 24, 2004